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Remarks:

This application was filed on 17.09.2020 as a divisional application to the application mentioned under INID code 62.

(54) ANTIBODY SPECIFICALLY BINDING TO ERBB3 AND USE THEREOF

(57) An antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof, and use thereof, are provided. The antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof may be effectively used to prevent or treat a disease related to activation or overexpression of ErbB3 protein.

Description

Technical Field

⁵ **[0001]** One or more example embodiments relate to an antibody specifically binding to a receptor tyrosine kinase ErbB3 protein or an antigen-binding fragment of the antibody, a method of preparing the same, and use thereof.

Background Art

[0002] The epidermal growth factor receptor (EGFR or ErbB) family of receptor tyrosine kinases includes ErbB1 (known also as epidermal growth factor receptor (EGFR)), ErbB2 (known also as human epidermal growth factor receptor 2 (HER2)), ErbB3 (known also as HER3), and ErbB4 (known also as HER4). The receptor tyrosine kinases of the ErbB family may form a homodimer or heterodimer by combination with a ligand and may activate the signal transduction pathway of mitogen-activated protein kinase kinase (MAP2K, MEK, or MAPKK)/ mitogen-activated protein kinase (MAPK), or the signal transduction pathway of phosphoinositide 3-kinase (PI3K)/ protein kinase B (PKB or Akt). The ErbB family of proteins is reported to be related to the occurrence, progress, or prognosis of cancer.

[0003] Erbitux® (Cetuximab) or Tarceva® (Erlotinib) as ErbB1 inhibitors and Herceptin® (Trastuzumab) or Tyverb® (Lapatinib) as ErbB2 inhibitors, are commercially available anti-cancer drugs. However, a large number of patients are unresponsive to these anti-cancer drugs, and these anti-cancer drugs are accompanied with development of resistance. A specific inhibitor antibody to ErbB3 or ErbB4 has not yet been made commercially available.

[0004] Therefore, there is a need for the development of new anti-cancer drugs that may cope with the genetic diversity of cancer and overcome resistance to anti-cancer drugs.

Disclosure of Invention

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Technical Problem

[0005] One or more example embodiments include an antibody specifically binding to ErbB3, or an antigen-binding fragment thereof.

[0006] One or more example embodiments include a pharmaceutical composition for prevention or treatment of a disease related to the activation or overexpression of ErbB3 protein.

[0007] One or more example embodiments include a method of prevention or treatment of a disease related to the activation or overexpression of ErbB3 protein in an individual.

35 Solution to Problem

[0008] This application claims the benefit of Korean Patent Application No. 10-2015-0173281, filed on December 7, 2015, in the Korean Intellectual Property Office.

[0009] Reference will now be made in detail to example embodiments, which are illustrated in the accompanying drawings, wherein like reference numerals refer to like elements throughout. In this regard, the present example embodiments may have different forms and should not be construed as being limited to the descriptions set forth herein. Accordingly, the example embodiments are merely described below, by referring to the figures, to explain aspects of the present description. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. Expressions such as "at least one of," when preceding a list of elements, modify the entire list of elements and do not modify the individual elements of the list.

[0010] According to an aspect of the present disclosure, an antibody specifically binding to ErbB3 or an antigen-binding fragment of the antibody includes:

a heavy chain variable region including at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 61 to 85, and 102;

a light chain variable region including at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 86 to 101, and 103; or

the heavy chain variable region and the light chain variable region.

[0011] There are five types of heavy chains denoted by γ , δ , α , μ , and ϵ . The type of heavy chain defines the class of antibody. The heavy chain types α and γ each chain consists of approximately 450 amino acids, whereas μ and ϵ each chain consists of approximately 550 amino acids. Each heavy chain has two regions, i.e., the variable region and the constant region.

[0012] There are two types of light chains denoted by λ and κ . Each light chain consists of approximately 211 to 217 amino acids. Each human antibody contains only one type of light chain. Each light chain contains two successive domains including one constant region and one variable region.

[0013] The variable region refers to a region of the antibody which binds to an antigen.

[0014] The heavy chain variable region may include: a complementarity-determining region-H1 (CDR-H1) including an amino acid sequence selected from the group consisting of SEQ ID. NOs: 61 to 68; a CDR-H2 including an amino acid sequence selected from SEQ ID NOs: 69 to 77, and 102; and a CDR-H3 including an amino acid sequence selected from SEQ ID NOs: 78 to 85. For example, the heavy chain variable region may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 1 to 30. The term "complementarity-determining region (CDR)" refers to a site of the variable region of an antibody that imparts binding specificity of the antibody or antigen-binding fragment thereof to an antigen.

[0015] The light chain variable region may include: a CDR-L1 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 87, and 103; a CDR-L2 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 88 to 93; and a CDR-L3 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 94 to 101. For example, the light chain variable region may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 to 60.

[0016] The antibody or the antigen-binding fragment thereof may include a heavy chain variable region selected from the group consisting of heavy chain variable regions CDR-H1, CDR-H2, and CDR-H3, which represent amino acid sequences listed in Table 5.

[Table 5]

No.	CDR-H1	CDR-H2	CDR-H3
1	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQ	DLHMGPEGPFDY (SEQ ID NO: 78)
		G (SEQ ID NO: 69)	
2	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
3	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQ	DLHMGPEGPFDY (SEQ ID NO: 78)
		G (SEQ ID NO: 71)	
4	DYDMS (SEQ ID NO: 61)	SIEPDFGSSYYADSVR	DLHMGPEGPFDY (SEQ ID NO: 78)
		G (SEQ ID NO: 72)	
5	DYDMS (SEQ ID NO: 61)	IIEPDSGSIYYADSVQG (SEQ ID NO: 73)	DLHMGPEGPFDY (SEQ ID NO: 78)
6	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQ	DRHMWPEGPFDY (SEQ ID NO: 79)
		G (SEQ ID NO: 71)	
7	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQ	DRHMWPEGPFDY (SEQ ID NO: 79)
		G (SEQ ID NO: 69)	
8	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQ	DRHMWPEGPFDY (SEQ ID NO: 79)
		G (SEQ ID NO: 69)	
9	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQ	DRHMWPEGPFDY (SEQ ID NO: 79)
		G (SEQ ID NO: 69)	
10	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
11	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
12	DYDMS (SEQ ID NO: 61)	SIEPDSGSTDYADSVQ	DRHMWPEGPFDY (SEQ ID NO: 79)
		G (SEQ ID NO: 74)	

(continued)

	No.	CDR-H1	CDR-H2	CDR-H3
5	13	DYDMS (SEQ ID NO: 61)	TIEPDSGSTYYADSVQ	DLHMGPEGPFDY (SEQ ID NO: 78)
			S (SEQ ID NO: 75)	
	14	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQ	DLHMGPEGPFDY (SEQ ID NO: 78)
10			G (SEQ ID NO: 69)	
	15	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQ	DLHMWPEGPFDY (SEQ ID NO: 80)
			G (SEQ ID NO: 71)	
15	16	DYDMS (SEQ ID NO: 61)	TIEPDYGSTLYADSVQ	DLHMGPEGPFDY (SEQ ID NO: 78)
			G (SEQ ID NO: 102)	
20	17	DYDMS (SEQ ID NO: 61)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
	18	WYDMT (SEQ ID NO: 62)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
25			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
	19	WYDLA (SEQ ID NO: 63)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
30	20	WYDMS (SEQ ID NO: 64)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
25	21	WYDIA (SEQ ID NO: 65)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
35			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
	22	WYDLS (SEQ ID NO: 66)	GISYDGGNTYYADSVK	DPSWCLQDLCYYADG
40			G (SEQ ID NO: 76)	MDV (SEQ ID NO: 81)
	23	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFVSDSTFDY (SEQ ID NO: 82)
	24	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFMSDSTFDY (SEQ ID NO: 83)
45	25	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
45	26	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
	27	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
	28	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
50	29	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
	30	YYDMS (SEQ ID: 68)	AIYYDSGSIYYADSAKG (SEQ ID: 77)	DRLFESDSTFDY (SEQ ID: 85)

[0017] For example, the antibody or the antigen-binding fragment thereof may include a heavy chain variable region that includes a CDR-H1 including an amino acid sequence of SEQ ID NO: 61, a CDR-H2 including an amino acid sequence of SEQ ID NO: 69, and a CDR-H3 including an amino acid sequence of SEQ ID NO: 78.

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[0018] The antibody or the antigen-binding fragment thereof may include a light chain variable region selected from the group consisting of light chain variable regions CDR-L1, CDR-L2, and CDR-L3, which include amino acid sequences

listed in Table 6.

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[Table 6]

5	No.	CDR-L1	CDR-L2	CDR-L3
	31	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	32	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	QGWDTSLSGHV (SEQ ID NO: 95)
	33	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
10	34	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	35	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	36	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
15	37	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNHRPS (SEQ ID NO: 90)	AAWDSSLSGYV (SEQ ID NO: 94)
	38	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	39	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
	40	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	VGWDSSLYGHV (SEQ ID NO: 96)
20	41	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLWGDV (SEQ ID NO: 97)
	42	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
	43	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
25	44	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLYVDV (SEQ ID NO: 98)
	45	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADNFRPS (SEQ ID NO: 91)	AAWDSSLSGYV (SEQ ID NO: 94)
	46	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLSGDF (SEQ ID NO: 99)
	47	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
30	48	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	49	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	50	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
35	51	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	52	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	53	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	54	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
40	55	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	56	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	57	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
45	58	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	59	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	60	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)

[0019] For example, the antibody or the antigen-binding fragment thereof may include a light chain variable region that includes a CDR-L1 including an amino acid sequence of SEQ ID NO: 86, a CDR-L2 including an amino acid sequence of SEQ ID NO: 88, and a CDR-L3 including an amino acid sequence of SEQ ID NO: 94.

[0020] The ErbB3 may be an ErbB3 polypeptide or a fragment thereof. The ErbB3 polypeptide may be a human amino acid sequence with GenBank Accession No. NP_001005915, or a mouse amino acid sequence with GenBank Accession No. NP_034283. The fragment of the ErbB3 polypeptide may be a polypeptide including a partial amino acid sequence of the ErbB3 polypeptide. The ErbB3 is a receptor tyrosine kinase of the epidermal growth factor receptor (EGFR or ErbB) family, and is known also as HER3.

[0021] The antibody or the antigen-binding fragment thereof that specifically binds to ErbB3 may have affinity to an ErbB3 polypeptide or a fragment thereof.

[0022] The antibody or the antigen-binding fragment thereof may inhibit binding of ErbB3 protein with a material that specifically binds to ErbB3 protein, dimerization of ErbB1 protein and ErbB3 protein, dimerization of ErbB3 protein and ErbB3 protein, phosphorylation of ErbB3 or Akt, or a combination thereof. The material specifically binding to ErbB3 protein may be heregulin (HRG).

[0023] The term "antibody" is interchangeably used with "immunoglobulin (Ig)." The whole antibody has a structure including two full-length light chains and two full-length heavy chains, which are connected by disulfide (SS) bonds. The antibody may be, for example, IgA, IgD, IgE, IgG, or IgM. The antibody may be a monoclonal antibody or a polyclonal antibody. The antibody may be an animal-derived antibody, a mouse-human chimeric antibody, a humanized antibody, or a human antibody.

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[0024] The term "antigen-binding fragment" refers to a fragment of the whole immunoglobulin structure, which may be a part of a polypeptide including an antigen-binding site. For example, the antigen-binding fragment may be scFv, $(scFv)_2$, Fv, Fab, Fab', Fv F(ab')₂, or a combination thereof.

[0025] The antibody or the antigen-binding fragment thereof may be modified. For example, the antibody or the antigen-binding fragment thereof may be modified by conjugation or binding, glycosylation, tag attachment, or a combination thereof. The antibody may be conjugated with other drugs such as anti-cancer drug. For example, the antibody or the antigen-binding fragment thereof may be conjugated with horseradish peroxidase (HRP), alkaline phosphatase, hapten, biotin, streptavidin, a fluorescent material, a radioactive material, quantum dots, polyethylene glycol (PEG), a histidine tag, or a combination thereof. The fluorescent material may be Alexa Fluor®532, Alexa Fluor®546, Alexa Fluor®568, Alexa Fluor®750, Alexa Fluor®790, or Alexa Fluor™ 350.

[0026] According to another aspect of the present disclosure, a pharmaceutical composition for prevention or treatment of a disease related to activation or overexpression of ErbB3 protein includes the antibody or the antigen-binding fragment thereof according to any of the above-described example embodiments.

[0027] The antibody, antigen-binding fragment, and ErbB3 protein are the same as described above.

[0028] The disease related to the activation or overexpression of ErbB3 protein may be cancer. The cancer may be a solid cancer or a non-solid cancer. Solid cancers refer to the incidence of cancerous tumors in solid organs such as the liver, lung, breast, or skin, whereas non-solid cancers refer to cancers affecting the blood, and so are called blood cancer. For example, the cancer may be selected from the group consisting of breast cancer, skin cancer, head and neck cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, gastric cancer, ovarian cancer, prostate cancer, bladder cancer, uterine cancer, liver cancer, kidney cancer, clear cell sarcoma, melanoma, cerebrospinal tumors, brain cancer, thymoma, mesothelioma, esophageal cancer, billiary tract cancer, testicular cancer, germinal cancer, thyroid cancer, parathyroid cancer, cervical cancer, endometrial cancer, lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, acute leukemia, chronic leukemia, multiple myeloma, Hodgkin's disease, endocrine cancer, and sarcoma. [0029] The term "prevention" refers to any act that suppresses or delays the onset of a disease related to the activation or overexpression of ErbB3 protein by administration of the pharmaceutical composition. The term "treatment" refers to any act that alleviates symptoms of a disease related to the activation or overexpression of ErbB3 protein by administration of the pharmaceutical composition.

[0030] The pharmaceutical composition may include a pharmaceutically acceptable carrier. The carrier may be construed as meaning an excipient, a diluent, or an adjuvant. For example, the carrier may be selected from the group consisting of lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia rubber, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, polyvinylpyrrolidone, water, physiological saline, a buffer such as phosphate-buffered saline (PBS), methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, glycine, histidine, serine, polysorbate, and mineral oil. The pharmaceutical composition may include a filler, an anti-coagulant, a lubricant, a wetting agent, a flavoring agent, an emulsifier, a preservative, or a combination thereof. [0031] The pharmaceutical composition may be formulated in any form using any common method in the art. For example, the pharmaceutical composition may be formulated in oral dosage form (for example, powders, tablets, capsules, syrups, pills, or granules), or parenteral dosage form (for example, injection). The pharmaceutical composition may be prepared in formulation for systemic delivery, or in a formulation for local delivery.

[0032] The pharmaceutical composition may further include an anti-cancer drug. The anti-cancer drug may be Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab, T-DM1, Pertuzumab, Lapatinib, Paclitaxel, Tamoxifen, Cisplatin, anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, 5-fluorouracil (5FU), Gemcitabine, or a combination thereof. The pharmaceutical composition may include a single composition or separate compositions. For example, the antibody or the antigen-binding fragment thereof of the pharmaceutical composition may be a composition in parenteral dosage form, and the anti-cancer drug may be a composition in oral dosage form.

[0033] The pharmaceutical composition may include an effective amount of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof. The term "effective amount" used herein refers to an amount sufficient to prevent or treat a disease related to activation or overexpression of ErbB3 protein when administered to an

individual who needs such prevention or treatment. The effective amount may be appropriately selected depending on a selected cell or individual by one of ordinary skill in the art. For example, the effective amount may be determined depending on disease severity, a patient's age, body weight, health conditions, gender, a patient's drug sensitivity, administration duration, administration route, excretion rate, treatment duration, and other factors, including use of a drug in combination with or at the same time as the pharmaceutical composition, and other factors known in the medical field. The effective amount may be about $0.5~\mu g$ to about 2~g, about $1~\mu g$ to about 1~g, about $1~\mu g$ to about 1~g, about 1~g to about 1~g0 mg, or about 1~g0 mg of the pharmaceutical composition.

[0034] A dose of the pharmaceutical composition may be, for example, about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 10 mg/kg, or about 0.1 mg/kg to about 1 mg/kg when administered to an adult. The number of administrations may be, for example, once or multiple times a day, once a week, once in two weeks, once in three weeks, once in four weeks, or once a year.

[0035] According to another aspect of the present disclosure, a method of prevention or treatment of a disease related to activation or overexpression of ErbB3 protein in an individual includes administering the antibody or an antigen-binding fragment thereof according to any of the above-described example embodiments to the individual.

[0036] The antibody, antigen-binding fragment, ErbB3 protein, disease related to the activation or overexpression of ErbB3 protein, prevention, or treatment may be the same as described above.

[0037] The individual may be a mammal, for example, a human, cow, horse, pig, dog, sheep, goat, or cat. The individual may be an individual who suffers from a disease related to the activation or overexpression of ErbB3 protein or who is susceptible to the disease, which may be cancer.

[0038] The method may further include administering an anti-cancer drug to the individual. The anti-cancer drug may be administered at the same time with, separately from, or sequentially with the antibody or an antigen-binding fragment thereof according to any of the above-described example embodiments.

[0039] For example, the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be directly administered to the individual by any method, for example, by oral, intravenous, intramuscular, transdermal, mucosal, intransal, intratracheal, or subcutaneous administration. The antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be administered systemically or locally. The antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be administered alone or together with a pharmaceutically active compound.

[0040] A dose of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may vary depending on a patient's condition, body weight, disease severity, drug formulation, administration route, and administration duration, and may be appropriately selected by one of ordinary skill in the art. For example, a dose of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 10 mg/kg, or about 0.1 mg/kg to about 1 mg/kg when administered to an adult. The number of administrations may be, for example, once or multiple times a day, once a week, once in two weeks, once in four weeks, or once a year.

[0041] According to another aspect of the present disclosure, a method of prevention or treatment of cancer drug resistance in an individual includes administering the antibody or the antigen-binding fragment of any one of claims 1 to 10 to the individual.

40 Brief Description of Drawings

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[0042] These and/or other aspects will become apparent and more readily appreciated from the following description of the example embodiments, taken in conjunction with the accompanying drawings in which:

- FIGS. 1a and 1b illustrate amino acid sequences and complementarity-determining regions (CDRs) in variable regions of heavy chains (FIG. 1a) and light chains (FIG. 1b) of lead antibodies and modified antibodies thereof;
 - FIG. 2 is a graph showing the binding affinity (%) of ErbB3 protein and HRG in the presence of anti-ErbB3 antibodies; FIG. 3 is a graph showing the binding affinity (%) of ErbB2 protein and ErbB3 protein in the presence of anti-ErbB3 antibodies;
- FIGS. 4a and 4b are graphs showing phosphorylation ratios (%) of ErbB3 and Akt, respectively, in the presence of anti-ErbB3 antibodies;
 - FIG. 5 is a graph of relative proliferation (%) of BxPC3 pancreatic cancer cells in the presence of anti-ErbB3 antibodies; FIG. 6 is a graph of tumor volume (mm³) in a BT474 breast cancer xenograft model after administration of anti-ErbB3 antibodies;
- FIG. 7 is a graph of tumor volume (mm³) in a MDA-MB-468 breast cancer xenograft model after administration of anti-ErbB3 antibodies;
 - FIG. 8 is a graph of tumor volume (mm³) in an A431 skin cancer xenograft model after administration of anti-ErbB3 antibodies;

FIG. 9 is a graph of tumor volume (mm³) in a FaDu head and neck cancer xenograft model after administration of anti-ErbB3 antibodies or combined administration of anti-ErbB3 antibodies and Cetuximab;

FIG. 10 is a graph of the activity of caspase 3/7 (in relative luminance units (RLU)) in breast cancer cells after combined administration of paclitaxel, HRG, and anti-ErbB3 antibody;

FIG. 11 is a graph of cancer cell proliferation rate (%) in colorectal cancer cells after combined administration of Cetuximab, HRG, and anti-ErbB3 antibody; and

FIG. 12 is a graph of tumor volume in an Cetuximab-resistant xenograft model after combined administration of Cetuximab and anti-ErbB3 antibody.

10 Mode for the Invention

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[0043] Hereinafter, one or more embodiments of the present disclosure will now be described in detail with reference to the following examples. However, these examples are only for illustrative purposes and are not intended to limit the scope of the one or more embodiments of the present disclosure.

Example 1. Preparation of anti-ErbB3 antibody

1. Screening of lead antibody

[0044] To obtain human anti-ErbB3 antibodies, the human synthetic scFv-phage display library (provided by H.B. SHIM of Ewha Womans University, Korea) was screened against ErbB3 protein (R&D systems) to obtain phage displaying scFv fragments that bind to ErbB3.

[0045] Nucleic acid sequences encoding the scFV fragments of the obtained phage were analyzed, and amino acid sequences of the VH and VL domains of the scFv fragments that bind to ErbB3 were identified by amino acid sequence analysis. After the sequences of the scFv fragments that bind to ErbB3 were obtained, the VH and VL domains were reconstructed using a Selexis 085 vector (Selexis) encoding IgG1, to thereby assemble the whole antibody gene. The reconstructed expression vectors encoding IgG1 were transformed and expressed at a small scale in Chinese hamster ovary (CHO) cell lines. The expressed anti-ErbB3 antibodies were subjected to measurement of binding affinity to ErbB3 and cellular-based analysis, to thereby screen anti-ErbB3 lead antibodies 442P, 472P, and 451P that inhibit heregulin (HRG)-dependent ErbB3 signal transduction.

2. Screening of modified antibodies from lead antibodies

[0046] Fab-phage display libraries were constructed by introducing mutations into six CDR sites of the screened anti-ErbB3 lead antibodies 442P, 472P, and 451P of Example 1.1 by random mutagenesis. The Fab-phage display libraries were amplified by polymerase chain reaction (PCR) with primers (by Integrated DNA Technologies, Inc.), which were made to order, and Phusion polymerase (New England Biolabs).

[0047] The constructed Fab-phage display libraries were screened against the recombinant human ErbB3 protein (R&D systems) to screen for antibodies with improved binding affinity to the recombinant human ErbB3, as compared with the lead antibodies. The screened antibodies were reconstructed to IgG as described in Example 1.1 and transformed and expressed at a small scale in CHO cell lines.

[0048] The binding affinity of the anti-ErbB3 antibodies was measured using an Octet® QK384 system (Pall Life Sciences). The antibodies with improved binding affinity compared to the lead antibodies were screened based on the results and subjected to cellular-based analysis to verify efficacy. Amino acid sequences of the variable regions of the anti-ErbB3 lead antibodies and the modified antibodies were analyzed, and complementarity-determining regions (CDRs) were determined according to the Kabat definition. The amino acid sequences (SEQ ID NOs: 1 to 60) in the various regions of heavy chains and light chains of the screened antibodies are presented in FIGS. 1a and 1b, and the amino acid sequences in the CDRs of the heavy chains and light chains are shown in Table 1 and 2, respectively.

[Table 1]

Antibod y	CDR-H1	CDR-H2	CDR-H3
442P	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
442S1	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)

(continued)

	Antibod y	CDR-H1	CDR-H2	CDR-H3
5	442S2	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMGPEGPFDY (SEQ ID NO: 78)
	442S4	DYDMS (SEQ ID NO: 61)	SIEPDFGSSYYADSVRG (SEQ ID NO: 72)	DLHMGPEGPFDY (SEQ ID NO: 78)
10	442S5	DYDMS (SEQ ID NO: 61)	IIEPDSGSIYYADSVQG (SEQ ID NO: 73)	DLHMGPEGPFDY (SEQ ID NO: 78)
	442S6	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DRHMWPEGPFDY (SEQ ID NO: 79)
15	442S9	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
	442S10	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
20	442M3	DYDMS (SEQ ID NO:	SIYPDSGSTYYADSVQG	DRHMWPEGPFDY
		61)	(SEQ ID NO: 69)	(SEQ ID NO: 79)
	442M4	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
25	442M5	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
	442M6	DYDMS (SEQ ID NO: 61)	SIEPDSGSTDYADSVQG (SEQ ID NO: 74)	DRHMWPEGPFDY (SEQ ID NO: 79)
30	442M7	DYDMS (SEQ ID NO: 61)	TIEPDSGSTYYADSVQS(SEQID NO: 75)	DLHMGPEGPFDY (SEQ ID NO: 78)
	442M8	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
35	442M10	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMWPEGPFDY (SEQ ID NO: 80)
	442M11	DYDMS (SEQ ID NO: 61)	TIEPDYGSTLYADSVQG(SEQIDNO: 102)	DLHMGPEGPFDY (SEQ ID NO: 78)
40	472P	DYDMS (SEQ ID	GISYDGGNTYYADSVKG (SEQ ID	DPSWCLQDLCYYADG
		NO: 61)	NO: 76)	MDV (SEQ ID NO: 81)
	472S1	WYDMT (SEQ ID	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG
45		NO: 62)	NO. 70)	MDV (SEQ ID NO: 81)
	472S2	WYDLA (SEQ ID NO: 63)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG
50		140.03)	NO. 70)	MDV (SEQ ID NO: 81)
50	472S3	WYDMS (SEQ ID NO: 64)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG
		NO. 04)	NO. 70)	MDV (SEQ ID NO: 81)
55	472S4	WYDIA (SEQ ID NO: 65)	GISYDGGNTYYADSVKG (SEQ ID	DPSWCLQDLCYYADG
		140.00)	NO: 76)	MDV (SEQ ID NO: 81)

(continued)

	Antibod y	CDR-H1	CDR-H2	CDR-H3
	472M1	WYDLS (SEQ ID NO: 66)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG
				MDV (SEQ ID NO: 81)
	451P	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFVSDSTFDY (SEQ ID NO: 82)
)	451M1	DYDMS (SEQ ID NO:	AIYYDSGSIYYADSAKG	DRLFMSDSTFDY (SEQ
		61)	(SEQ ID NO: 77)	ID NO: 83)
5	451M2	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
	451M3	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
)	451M4	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
	451M5	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
5	451M6	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
	451M7	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)

[Table 2]

	Antibod y	CDR-L1	CDR-L2	CDR-L3
35	442P	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	442S1	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	QGWDTSLSGHV (SEQ ID NO: 95)
40	442S2	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	442S4	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
45	442S5	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	442S6	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
50	442S9	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNHRPS (SEQ ID NO: 90)	AAWDSSLSGYV (SEQ ID NO: 94)
	442S10	SGSSSNIGSNSVS (SEQID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
55	442M3	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
	442M4	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	VGWDSSLYGHV (SEQ ID NO: 96)

(continued)

	Antibod y	CDR-L1	CDR-L2	CDR-L3
5	442M5	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLWGDV (SEQ ID NO: 97)
	442M6	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
10	442M7	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
	442M8	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLYVDV (SEQ ID NO: 98)
15	442M10	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADNFRPS (SEQ ID NO: 91)	AAWDSSLSGYV (SEQ ID NO: 94)
	442M11	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLSGDF (SEQ ID NO: 99)
20	472P	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	472S1	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
25	472S2	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	472S3	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
30	472S4	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
	472M1	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
35	451P	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	451M1	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
40	451M2	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	451M3	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
45	451M4	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	451M5	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
50	451M6	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
	451M7	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)

Example 2. In-vitro effect of anti-ErbB3 antibody

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1. Binding affinity of anti-ErbB3 antibody to human ErbB3 protein

[0049] Binding affinities of the screened antibodies (Example 1.2) to ErbB3 protein (antigen) were measured. [0050] In particular, the binding affinities of the anti-ErbB3 antibodies to the recombinant human ErbB3 protein (R&D systems) and the antigen-antibody interactive dynamics were measured using an Octet® QK384 system (Pall Life Sciences). After activation of carboxyl groups in 20 mM of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 40 mM of N-hydroxysulfosuccinimide (sulfo-NHS) solution on an AR2G sensor (ForteBio), 10 μg/mL of human ErbB3 protein solution diluted with 10 mM of sodium acetate (pH 4.0) (ForteBio) was added to immobilize human ErbB3 protein onto the AR2G sensor. The AR2G sensor to which the human ErbB3 protein was immobilized was treated with 1 M of ethanolamine (ForteBio) to inactivate the remaining unreacted carboxyl groups. 12.5 nM, 25 nM, and 50 nM antibody solutions were each added onto the AR2G sensor and then the binding phase of the reaction product was observed for about 900 seconds. Next, a 1x kinetics buffer (ForteBio) was added to the reaction product, and the dissociation phase of the reaction product was observed for about 1200 seconds, followed by determination of an association constant (ka), a dissociation constant (kd), and an equilibrium dissociation constant (KD) of each type of antibody with Octet® analysis software (Pall Life® Sciences).

	antibody with Octet® analysis software (Pall Life® Sciences).				
			[Tab	le 3]	
20		Antibody	KD (M)	ka(1/Ms)	kd(1/s)
		442P	2.83E-10	1.25E+06	3.52E-04
		442S1	<1.0E-12	5.22E+05	3.94E-07
25		442S2	7.11E-11	1.17E+06	8.28E-05
		442S4	3.71E-11	1.48E+06	5.47E-05
		442S5	1.75E-11	1.57E+06	2.74E-05
		442S6	<1.0E-12	8.72E+05	<1.0E-07
30		442S9	7.16E-11	8.21 E+05	5.87E-05
		442S10	1.14E-10	8.14E+05	9.29E-05
		442M3	3.40E-12	7.71E+05	2.62E-06
35		442M4	<1.0E-12	5.73E+05	<1.0E-07
		442M5	<1.0E-12	6.65E+05	<1.0E-07
		442M6	2.01 E-11	9.69E+05	1.95E-05
		442M7	2.91 E-11	1.56E+06	4.55E-05
40		442M8	2.56E-12	8.70E+05	2.23E-06
		442M10	<1.0E-12	4.71 E+05	<1.0E-07
		442M11	5.43E-12	1.49E+06	8.09E-06
45		472P	2.84E-10	1.79E+06	5.08E-04
		472S1	<1.0E-12	6.49E+05	3.33E-07
		472S2	<1.0E-12	1.07E+06	<1.0E-07
50		472S3	<1.0E-12	5.22E+05	1.43E-07
50		472S4	9.41E-12	1.15E+06	1.09E-05
		472M1	1.25E-11	1.39E+06	1.74E-05
		451P	5.35E-11	1.18E+06	6.33E-05
55		451M1	2.48E-11	1.24E+06	3.08E-05
		451M2	1.26E-11	1.24E+06	1.56E-05
		1			

451M3

1.87E+06

2.30E-07

<1.0E-12

(continued)

Antibody	KD (M)	ka(1/Ms)	kd(1/s)
451M4	6.12E-12	2.01 E+06	1.23E-05
451M5	2.17E-11	1.52E+06	3.29E-05
451M6	3.47E-12	1.20E+06	4.17E-06
451M7	4.92E-12	1.35E+06	6.63E-06

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[0051] Referring to Table 3, the selected antibodies were found to have an equilibrium dissociation constant (KD) of about 0.1 nM to about 0.1 pM, indicating high binding affinities to the recombinant human ErbB3 protein.

2. ErbB3 protein-HRG binding inhibitory ability of anti-ErbB3 antibody

[0052] Whether the selected antibodies of Example 1.2 inhibit binding of ErbB3 protein and HRG as a ligand thereof was investigated.

[0053] In particular, a binding affinity of HRG (R&D systems) to human ErbB3 protein (R&D systems) was measured using an Octet® QK384 system (Pall Life Sciences). After 10 μ g/mL of HRG protein was immobilized onto an AR2G sensor according to the same method as used in Example 2.1, the remaining unreacted carboxyl groups were inactivated using a 1M ethanolamine (ForteBio). Next, a mixed solution of 5 μ g/mL of human ErbB3 protein (R&D systems) and 10 nM or 100 nM of anti-ErbB3 antibodies was added onto the AR2G sensor with the HRG protein immobilized thereon, and then the binding phase was observed for about 900 seconds. A reaction product to which no anti-ErbB3 antibodies were added was used as a negative control group. The amount of the remaining human ErbB3 protein bound to the HRG protein immobilized to the AR2G sensor was measured. A binding affinity (%) of ErbB3 protein and HRG in the presence of the anti-ErbB3 antibodies with respect to the negative control group was calculated. The results are shown in FIG. 2, in which the Y-axis represents a binding affinity (%) relative to the negative control group, and the X-axis represents antibodies at different concentrations of 0 nM, 10 nM, and 100 nM.

[0054] Referring to FIG. 2, the selected antibodies were found to inhibit binding of human ErbB3 protein and HRG protein, depending on the concentrations of the antibodies, whereas the hlgG control group showed no effect on the binding of ErbB3 and HRG.

3. ErbB2-ErbB3 dimerization inhibition ability of anti-ErbB3 antibody

[0055] An investigation was carried out to assess the ability of the selected antibodies of Example 1. 2 to inhibit dimerization of ErbB2 protein and ErbB3 protein.

[0056] In particular, 100 $\mu\ell$ of recombinant human ErbB2 protein (1 μ g/mL) was applied to a multi-array 96-well plate (Thermo scientific) and incubated at 4°C for about 16 hours to coat the ErbB2 protein on the multi-array 96-well plate. 200 $\mu\ell$ of 5% (w/v) BSA/PBS solution was applied to the coated plate and incubated at 37°C for about 1 hour. A mixture of 50 $\mu\ell$ of the recombinant human ErbB3 protein (0.6 μ g/mL) and 50 $\mu\ell$ of the selected anti-ErbB3 antibodies (0.2 μg/mL) was applied to the plate and the reaction mixture was incubated at 37°C for about 2 hours. The resulting plate was washed three times with 0.05%(v/v) Tween/PBS solution. 100 $\mu\ell$ of goat-anti-ErbB3 polyclonal antibody (1 μ g/mL, R&D systems) was applied to the washed plate and incubated at 37°C for about 1 hour. The plate was then washed three times with a 0.05%(v/v) Tween/PBS solution. 100 $\mu\ell$ of anti-goat Fc-horseradish peroxidase (HRP) (Jackson Immunoresearch), diluted at 1:5000 with a 5% (w/v) BSA/PBS solution, was applied to the plate and then incubated at 37° C for about 1 hour. The plate was then washed three times with a 0.05%(v/v) Tween/PBS solution. 100 $\mu\ell$ of 3,3',5,5'tetramethylbenzidine (TMB) as a substrate was applied to each well and incubated at room temperature for about 5 minutes, followed by terminating the reaction with 100 $\mu\ell$ of a 2N sulfuric acid solution. A reaction mixture to which no anti-ErbB3 antibodies were added was used as a negative control group. The absorbance of the plate at a wavelength of 450 nm was measured. The binding affinities of ErbB2 protein and ErbB3 protein under the presence of anti-ErbB3 antibodies were calculated from the measured absorbance. Human IgG, which does not bind to ErbB3, was used as another negative control group.

[0057] The binding affinities (%) of ErbB2 protein and ErbB3 protein in the presence of anti-ErbB3 antibodies with respect to the negative control group were calculated. The results are shown in FIG. 3, wherein the Y-axis denotes a binding affinity (%) relative to the negative control group, and hlgG denotes human lgG.

[0058] Referring to FIG. 3, the selected antibodies were found to inhibit the dimerization of ErbB2 protein and ErbB3 protein, whereas the hlgG control group did not demonstrate any inhibition of dimerization.

4. ErbB3 and Akt phosphorylation inhibition ability of anti-ErbB3 antibody

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[0059] An investigation was carried out to assess the ability of the selected antibodies of Example 1. 2 to inhibit phosphorylation of ErbB3 protein and Akt.

[0060] In particular, about 5x10⁵ MCF7 breast cancer cells (from the National Institutes of Health) were inoculated onto a 24-well plate, and Roswell Park Memorial Institute (RPMI)-1640 medium (Invitrogen) including penicillin-streptomycin antibiotic (Invitrogen) and 10%(v/v) of fetal bovine serum (FBS) was added to the cells on the 24-well plate and incubated at 37°C under 5% CO₂ conditions for about 24 hours. Next, the medium was exchanged with fresh RPMI-1640 medium, and the cells were cultured under serum starving conditions for about 24 hours. Next, the selected anti-ErbB3 antibodies were added to the cells and incubated at 37°C under 5% CO₂ conditions for about 2 hours. The antibodies 442P and 472P were each added to the cells at concentrations of about 67 nM, 13 nM, 3 nM, 534 pM, 107 pM, 21 pM, and 4 pM, while the antibodies 442S1, 442S5, 442M6, 472S2, and 472M1 were added to the cells at concentrations of 13 nM, 3 nM, 834 pM, 208 pM, 52 pM, and 13 pM. After 1 hours and 45 minutes, HRG was added to the cells and incubated at 37°C under 5% CO₂ conditions for about 15 minutes to stimulate the cells (total antibody treatment time: 2 hours). The cells were washed with cooled PBS and Cell Lysis Solution (Cell Signaling Technology) was added to thereby collect the cells. After quantification of protein in the selected cells was performed by BCA assay, phosphorylation levels of ErbB3 or Akt were analyzed.

[0061] The phosphorylation level of ErbB3 was assayed using a Phospho-ErbB3 Detection Kit (Cell Signaling Technology). After binding the cell protein to an ErbB3 antibody-coated ELISA plate, phosphotyrosine mouse detection antibody and HRP-conjugated anti-mouse antibody were developed on the ELISA plate. Next, tetramethylbenzidine (TMB) substrate was added to the reaction product, the reaction was stopped with reaction stop solution of the kit, and absorbance was measured with a plate reader.

[0062] The phosphorylation level of Akt1 was assayed using a Phospho-Akt1 Detection Kit (Cell Signaling Technology). After binding the cell protein to an anti-phosphoserine-coated ELISA plate, Akt1-specific detection antibody and HRP-conjugated antibody were developed on the ELISA plate. Next, after reaction with TMB substrate, the reaction was stopped with Reaction Stop Solution of the kit, and absorbance was measured with a plate reader.

[0063] FIGS. 4a and 4b are graphs of ErbB3 and Akt phosphorylation ratios, respectively, with respect to antibody concentration, plotted based on the measured absorbance. The half maximal inhibitory concentrations (IC_{50}) of the antibodies were calculated. The results are shown in Table 4.

[Table 4]

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[0064] Referring to FIGS. 4a and 4b and Table 4, the selected antibodies were found to inhibit phosphorylation of ErbB3 and Akt.

[0065] Similarly, it was also found that the selected antibodies inhibit phosphorylation of ErbB3 and Akt in breast cancer cell lines MDA-MB-468 and BT474, skin cancer cell line A431, pancreatic cancer cell line BxPC3, head and neck cancer cell line FaDu, lung cancer cell line A549, colorectal cancer cell line LoVo, melanoma cell line MALME-3M, ovarian cancer cell line OVCAR-8, and prostate cancer cell line DU145.

5. Pancreatic cancer cell line BxPC3 proliferation inhibition ability of anti-ErbB3 antibody

[0066] An investigation was carried out to assess the ability of the selected antibodies of Example 1.2 to inhibit proliferation of BxPC3 pancreatic cancer cells.

[0067] In particular, about $1x10^4$ BxPC3 pancreatic cancer cells (American Type Culture Collection) were inoculated onto a 96-well plate, and RPMI-1640 medium (Invitrogen) including 10% FBS was added to the cells on the 96-well plate and incubated at 37° C under 5% CO $_2$ conditions for about 24 hours. Next, the medium was exchanged with an RPMI-1640 medium including 0.1%(v/v) FBS. $0.02~\mu\text{g/mL}$, $0.2~\mu\text{g/mL}$, $0.2~\mu\text{g/mL}$, and $0.2~\mu\text{g/mL}$ of the 442S1 antibody or 442M6 antibody were added to the incubated cells and cultured at $0.2~\mu\text{g/mL}$ cunder $0.2~\mu\text{g/mL}$ conditions for about 2 hours. 50 ng/mL of HRG was further added to the cultured cells and incubated at $0.2~\mu\text{g/mL}$ cunder $0.2~\mu\text{g/mL}$ conditions for about 120 hours. Cultured cells without added antibodies were used as a negative control group. The number of viable cells was measured using a CellTiter-Glo Luminescent Cell Viability Assay (Promega). The relative proliferation rates were calculated based on the measured results. The results are shown in FIG. 5.

[0068] Referring to FIG. 5, the selected antibodies were found to inhibit proliferation of BxPC3 pancreatic cancer cells in a concentration-dependent manner.

Example 3. in-vivo effect of anti-ErbB3 antibody

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1. Tumor growth inhibition using BT474 breast cancer xenograft model

[0069] An investigation was carried to assess the ability of the selected antibodies of Example 1.2 to inhibit growth of tumors in a breast cancer cell xenograft animal model.

[0070] In particular, human breast cancer BT474 cells (American Type Culture Collection) were cultured in Dulbecco's Modified Eagle's *medium* (DMEM) medium (Hyclone) including 10% FBS. 17 β-estradiol-sustained release pellets (0.36 mg/60 days, Innovative Research of America) were subcutaneously inoculated into female NOD/SCID mice (HFK Bio-Technology Co. Ltd.) one day before the inoculation of cancer cells to maintain blood estrogen level. About $1x10^7$ of BT474 cancer cells were suspended in $100 \mu \ell$ of PBS containing 50% Matrigel, and the suspended cancer cells were injected into the fat tissue under a nipple of each mouse. Weights of the mice were measured twice a week, and the tumor volume was calculated using the equation of "0.5 a x b^2 ", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about 210 mm³ after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 6.

[0071] Referring to FIG. 6, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

2. Tumor growth inhibition using MDA-MB-468 breast cancer xenograft model

40 [0072] Human breast cancer cells MDA-MB-468 (American Type Culture Collection) were incubated in an L-15 medium (Hyclone) including 10%(v/v) of fetal bovine serum. About 5x10⁶ cancer cells were suspended in 100 μℓ of PBS including 50% Matrigel and subcutaneously injected into the flank region of female Nu/Nu mice (Vital River laboratories, Ltd). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 a x b²", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about 210 mm³ after 7 days from the injection of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 7.

[0073] Referring to FIG. 7, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

3. Tumor growth inhibition using A431 skin cancer xenograft model

[0074] Human skin cancer A431 cells (American Type Culture Collection) were incubated in DMEM medium (Hyclone) including 10% FBS. About 5x10⁶ cancer cells were suspended in 100 μℓ of PBS including 50% of Matrigel and subcutaneously injected into the flank region of female Balb/c nude mice (HFK Bio-Technology Co. Ltd.). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 a x b²", where a and b

were the long and short diameters of the tumor, respectively. When the tumor volume reached about 160 mm³ after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 8.

[0075] Referring to FIG. 8, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

4. Tumor growth inhibition using tumor xenograft model

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[0076] The antibody 442S1 was administered into FaDu head and neck cancer, pancreatic cancer, or lung cancer animal model, and the antibodies 442P or 472P antibodies were administered into gastric cancer animal model, in the same manner as described in Examples 3.1 to 3.3. As a result, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

Example 4. Effect of combined administration of anti-cancer drug and anti-ErbB3 antibody

[0077] An investigation was carried out to assess the ability of combined use of the antibodies 442S1 and Cetuximab to improve anti-cancer effects in FaDu head and neck cancer model.

[0078] Human head and neck cancer FaDu cells (Shanghai Institutes for Biological Sciences) were incubated in EMEM medium (Hyclone) including 10% FBS. About $5x10^6$ cancer cells were suspended in $100~\mu\ell$ of PBS including 50% Matrigel and subcutaneously injected into the flank region of the female NOD/SCID mice (HFK Bio-Technology Co. Ltd). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 a x b^2 ", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about $150~mm^3$ after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 4 groups, each including 10 mice. PBS (negative control group), antibodies 442S1 and Cetuximab (Merck) were administered into the tail veins of the mice in each group twice a week at a dose of 5 mg/kg of body weight for 4 weeks. In a combined use treatment group, antibodies 442S1 and Cetuximab were administered into the tail veins of the mice twice a week at a dose of 5 mg/kg of body weight for 4 weeks. Then, no antibodies were administered for one week. The tumor sizes were measured twice a week. The volume of the tumors after the administration of the antibodies or the combined administration was calculated. The results are shown in FIG. 9, in which down arrows (\downarrow) denote time injecting cancer cells, and *** denotes results of Tukey's multiple comparison test after one-way ANOVA (p<0.001).

[0079] Referring to FIG. 9, in the combined use of antibodies 442S1 and Cetuximab treatment group, the tumor volume was reduced from the initial administration stage and was about 68 mm³ on average at the end of the test (n=10/group). Accordingly, the combined administration of the selected antibody and Cetuximab was found to improve anti-cancer efficacy.

Example 5. Anti-cancer drug resistance improvement effect of anti-ErbB3 antibody

1. Paclitaxel resistance improvement effect in breast cancer

[0080] Apoptotic effects of Paclitaxel in breast cancer cell line ZR-75-30 may be reduced in the presence of HRG due to the activation of an ErbB3 signal transduction pathway (Wang S. et al., Oncogene, 29, 4225-4236, 2010). An investigation was carried out to assess the ability of the screened antibodies to improve resistance to Paclitaxel used as an anti-cancer drug and impart an anti-cancer effect.

[0081] About 1×10^4 ZR-75-30 cells (American Type Culture Collection) were inoculated onto a plate and incubated in RPMI 1640 medium (Invitrogen) including 10%(v/v) FBS at 37° C under 5% CO $_2$ conditions for about 24 hours. The medium was then exchanged with fresh medium (100 ng/mL HRG added) including 0.1%(v/v) FBS, and further incubation was performed at 37° C under 5% CO $_2$ conditions for about 24 hours. 10 nM of Paclitaxel (Bristol-Myers Squibb) and 25 μ g/mL of antibody 442S1 were added to the cultured cells and incubated at 37° C under 5% CO $_2$ conditions for about 72 hours. The cultured cells were collected, and the activity of caspase 3/7 as an apoptotic marker was measured using a Caspase 3/7 Substrate Assay (Promega). The measured activity of caspase 3/7 is shown in FIG. 10, in which RLU denotes relative luminescence units, and ** denotes t-test results (p < 0.01).

[0082] Referring to FIG. 10, the activity of caspase 3/7 was reduced by Paclitaxel, but was improved by the combined treatment of Paclitaxel and antibody 442S1, compared with the treatment with Paclitaxel alone (n=3). Accordingly, it was found that the apoptotic effect of Paclitaxel may be reduced in the presence of HRG, but recovered by administration of antibody 442S1.

2. Cetuximab resistance improvement effect in colorectal cancer

[0083] Cetuximab is effective in suppressing cancer cell proliferation in DiFi colorectal cancer cells, but loses its efficacy in the presence of HRG due to the activation of an ErbB3 signal transduction pathway. An investigation was carried out to assess the ability of the screened antibodies to overcome resistance to Cetuximab and impart cancer cell proliferation suppression effects.

[0084] In particular, DiFi colon cancer cells were incubated in RPMI-1640 medium (Invitrogen) including an antibiotic (Penicillin-Streptomycin, Invitrogen) and 10% FBS. About $1x10^4$ DiFi cells were inoculated onto a 96-well plate and incubated at 37°C under 5% CO_2 conditions for about 24 hours. Cetuximab and anti-ErbB3 antibody were mixed together in equal concentrations of 200 μ g/mL to obtain an Cetuximab/anti-ErbB3 antibody solution, which was then mixed with an equal amount of HRG (40 ng/mL). The Cetuximab/anti-ErbB3 antibody/HRG solution was applied to a 96-well plate and incubated at 37°C under 5% CO_2 conditions for about 72 hours. Cells cultured without antibodies and HRG were used as a negative control group. The number of viable cells was measured using a CellTiter-Glo luminescent cell viability assay (Promega). Cell proliferation rates were calculated based on the measured results. The results are shown in FIG. 11, in which *** denotes t-test results (p<0.001).

[0085] Referring to FIG. 11, the cell proliferation suppression effect of Cetuximab was reduced in the presence of HRG, but recovered in the treatment group which received Cetuximab and 442S1 antibodies in combination. Accordingly, it was found that the cell proliferation suppression effect of Cetuximab may be reduced in the presence of HRG, i.e., an ErbB3 ligand, but may be recovered by 442S1 antibodies blocking the HRG-ErbB3 signaling pathway.

3. Improvement in resistance to Cetuximab in Cetuximab resistant xenograft model

[0086] FaDu human head and neck cancer cells (Shanghai Institutes of Biological Sciences) were incubated in EMEM medium (Hyclone) including 10% FBS (Invitrogen), 0.01 mM NEAA (Non-Essential Amino Acid, Hyclone), and 2 mM L-glutamine (Invitrogen). About $5x10^6$ FaDu cancer cells were suspended in $100~\mu\ell$ of PBS and then subcutaneously injected into the frank region of the female NOD SCID mice (HFK Bio-Technology Co., Ltd.). Weights of the mice were measured twice a week, and tumor volume was calculated using the equation of "0.5 a x b^2 ", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about $165~mm^3$ after 8 days from the inoculation of the cancer cells, the mice were randomly selected. PBS (negative control group) or Cetuximab was administered into the tail veins of the mice in each group twice a week at a dose of 5~mg/kg of weight for 6.5~weeks. When the tumor growth suppression effect of Cetuximab was not maintained such that tumor volume increased to about 840 mm³, ten mice were randomly selected from each group, and 5~mg/kg of Cetuximab, 10~mg/kg of antibody 442S1 or combination of 5~mg/kg of Cetuximab and 10~mg/kg of antibody 442S1 was administered to the mice twice a week for 2~weeks. Tumor volumes were measured twice a week. The results are shown in FIG. 12.

[0087] Referring to FIG. 12, it was found that a significant tumor suppression effect was observed in the treatment group that received antibody 442S1 alone or antibody 442S1 and Cetuximab in combination, compared with the treatment group that received Cetuximab alone, indicating that antibody 442S1 may overcome resistance to Cetuximab and suppress tumor growth.

[0088] As described above, according to the one or more example embodiments, an antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof, and use thereof, are provided. The antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof may be effectively used to prevent or treat a disease related to activation or overexpression of ErbB3 protein.

[0089] It should be understood that example embodiments described herein should be considered in a descriptive sense only and not for purposes of limitation. Descriptions of features or aspects within each example embodiment should typically be considered as available for other similar features or aspects in other embodiments.

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35 40	<223> <400> Glu Val 1 Ser Leu Asp Met Ser Ser 50 Gln Gly	14 Gln I Arg I Ser I 35 Ile I	Leu Leu Se 20 Prp Va	eu Glu 5 er Cys al Arg ro Asp hr Ile	Ser Ala Gln Ser 55	Gly Ala Ala 40 Gly Arg	Gly Ser 25 Pro Ser	Gly 10 Gly Thr	Leu Phe Lys Tyr Ser 75	Val Thr Gly Tyr 60	Gln Phe Leu 45 Ala Asn	Pro Ser 30 Glu Asp	15 Asp Trp Ser	Tyr Val Val Tyr 80
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	Ser Leu	Arg Leu S	Ser Cys A	ala Ala Ser 25	Gly Phe Thr	Phe Ser Asp Tyr
15	Asp Met	Ser Trp V	al A rg G	In Ala Pro 40	Gly Lys Gly	Leu Glu Trp Val 45
	Ser Ser 50	Ile Tyr P		Ser Gly Ser 55	Thr Asp Tyr 60	Ala Asp Ser Val
20	Gln Gly 65	Arg Phe I	Thr Ile S 70	er Arg Asp	Asn Ser Lys 75	Asn Thr Leu Tyr 80
	Leu Gln	Met Asn S	Ser Leu A 85	arg Ala Glu	Asp Thr Ala 90	Val Tyr Tyr Cys 95
25	Ala Lys	Asp Leu H	His Met T	rp Pro Glu 105	Gly Pro Phe	Asp Tyr Trp Gly 110
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45	Asp Met	Ser Trp V	/al Arg G	In Ala Pro 40	Gly Lys Gly	Leu Glu Trp Val 45
50	Ser Thr 50	Ile Glu F	-	yr Gly Ser 55	Thr Leu Tyr 60	Ala Asp Ser Val
	Gln Gly 65	Arg Phe I	Thr Ile S 70	er Arg Asp	Asn Ser Lys 75	Asn Thr Leu Tyr 80
55	Leu Gln	Met Asn S	Ser Leu A 85	arg Ala Glu	Asp Thr Ala 90	Val Tyr Tyr Cys 95
	Ala Lys	Asp Leu H	lis Met G	Sly Pro Glu	Gly Pro Phe	Asp Tyr Trp Gly

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	Ser Leu	Arg Leu 20	Ser Cys	Ala Ala	Ser Gly P 25	he Thr Phe Ser	Asp Tyr
20	Asp Met	Ser Trp	Val Arg	Gln Ala 40	Pro Gly L	ys Gly Leu Glu 45	Trp Val
25	Ser Gly 50	Ile Ser	Tyr Asp	Gly Gly 55	Asn Thr T	yr Tyr Ala Asp 60	Ser Val
20	Lys Gly 65	Arg Phe	Thr Ile	Ser Arg	Asp Asn S	er Lys Asn Thr 75	Leu Tyr 80
30	Leu Gln	Met Asn	Ser Leu 85	Arg Ala	Glu Asp T	hr Ala Val Tyr	Tyr Cys 95
	Ala Arg	Asp Pro 100	Ser Trp	Cys Leu	Gln Asp L	eu Cys Tyr Tyr 110	Ala Asp
35	Gly Met	Asp Val 115	Trp Gly	Gln Gly 120	Thr Leu V	al Thr Val Ser 125	Ser
40	<210> <211> <212> <213>	18 127 PRT Artific	cial Seq	uence			
45	<220> <223>	Heavy (chain va	riable r	egion of a	ntibody 472S1	
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55	Asp Met	Thr Trp 35	Val Arg	Gln Ala 40	Pro Gly L	ys Gly Leu Glu 45	Trp Val
	Ser Gly	Ile Ser	Tyr Asp	Gly Gly	Asn Thr T	yr Tyr Ala Asp	Ser Val

	50	55	60	
	Lys Gly Arg Phe 65	Thr Ile Ser Arg Asp	p Asn Ser Lys Asn Tl 75	hr Leu Tyr 80
5	Leu Gln Met Asn	Ser Leu Arg Ala Glu 85	u Asp Thr Ala Val Ty 90	yr Tyr Cys 95
10	Ala Arg Asp Pro 100	Ser Trp Cys Leu Gl:	n Asp Leu Cys Tyr Ty 5	yr Ala Asp 10
	Gly Met Asp Val 115	Trp Gly Gln Gly The	r Leu Val Thr Val Se 125	er Ser
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30	Ser Leu Arg Leu 20	Ser Cys Ala Ala Se	r Gly Phe Thr Phe Se 5	er Trp Tyr 30
	Asp Leu Ala Trp 35	Val Arg Gln Ala Pro	o Gly Lys Gly Leu G 45	lu Trp Val
35	Ser Gly Ile Ser 50	Tyr Asp Gly Gly Ass 55	n Thr Tyr Tyr Ala As 60	sp Ser Val
	Lys Gly Arg Phe 65	Thr Ile Ser Arg Asp 70	p Asn Ser Lys Asn Tl 75	hr Leu Tyr 80
40	Leu Gln Met Asn	Ser Leu Arg Ala Glu 85	u Asp Thr Ala Val Ty 90	yr Tyr Cys 95
	Ala Arg Asp Pro 100	Ser Trp Cys Leu Gla 10	n Asp Leu Cys Tyr Ty 5 1:	yr Ala Asp 10
45	Gly Met Asp Val 115	Trp Gly Gln Gly The	r Leu Val Thr Val Se 125	er Ser
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	Asp	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 4 5	Glu	Trp	Val
10	Ser	Gly 50	Ile	Ser	Tyr	Asp	Gly 55	Gly	Asn	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
15	65	_	Arg			70			_		75	_				80
			Met		85					90					95	_
20			Asp	100					105					110		Asp
	Gly	Met	Asp 115	Val	Trp	Gly	Gln	Gly 120	Thr	Leu	Val	Thr	Val 125	Ser	Ser	
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	<210 <211		21 127	7												
		_														
	<212	2>	PRI													
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35 40	<213 <220 <223 <400 Glu 1 Ser Asp	3>)> 3> Val Leu Ile Gly 50	Head 21 Gln Arg Ala 35	Leu Leu 20 Trp	Leu 5 Ser Val	Glu Cys Arg	Ser Ala Gln Gly 55	Gly Ala Ala 40	Gly Ser 25 Pro	Gly 10 Gly Gly	Leu Phe Lys Tyr	Val Thr Gly Tyr 60	Gln Phe Leu 45	Pro Ser 30 Glu Asp	15 Trp Trp Ser	Tyr Val Val
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	-		•			20
	Ser Leu	Arg Leu Sei	Cys Ala	Ala Ser Gly	Phe Thr Phe Se	r Trp Tyr
		20		25	30	0
15		~	- ~-		- 61 - 61	
	Asp Leu	Ser Trp Val	. Arg Gin		Lys Gly Leu Gl	u Trp Val
		33		40	45	
	Ser Gly	Ile Ser Tyr	Asp Gly	Gly Asn Thr	Tyr Tyr Ala Asj	o Ser Val
20	50	-	55	-	60	•
20						
		Arg Phe Thi		Arg Asp Asn	Ser Lys Asn Th	-
	65		70		75	80
	Leu Gln	Met Asn Ser	Leu Arg	Ala Glu Asp	Thr Ala Val Ty	r Tvr Cvs
25		85	_	90		95
	Ala Arg	_	Trp Cys	_	Leu Cys Tyr Ty:	_
		100		105	110	0
	Clw Met	Aco Val Trr	Cly Cln	Cly Thr Lau	Val Thr Val Co	r Car
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	Com Tou	Ame Tou Co.	Com Nin	Ala Cam Clas	Dhe Mhe Dhe Co	
	ser Leu	arg Leu Sei	Cys Ala	Ala Ser Gly	Phe Thr Phe Se:	
		20		23	3.	•
50	Asp Met	Ser Trp Val	Arg Gln	Ala Pro Gly	Lys Gly Leu Gl	u Trp Val
		35	_	40	45	_
		Ile Tyr Tyr	_	Gly Ser Ile	Tyr Tyr Ala Ası	p Ser Ala
	50		55		60	
55	Lys Glv	Arg Phe Thi	: Ile Ser	Arg Asp Asn	Ser Lys Asn Th	r Leu Tvr
	65	<u> </u>	70	3 <u>F</u>	75	80

	Leu Gln Me	t Asn Ser 85		Ala Glu Asp		l Tyr Tyr Cys 95
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	Ser Leu Ar	g Leu Ser 20	Cys Ala	Ala Ser Gly 25	Phe Thr Ph	e Ser Asp Tyr 30
25	_	r Trp Val	Arg Gln	Ala Pro Gly 40		u Glu Trp Val 5
	Ser Ala II 50	e Tyr Tyr	Asp Ser 55	Gly Ser Ile	Tyr Tyr Al 60	a Asp Ser Ala
30	Lys Gly Ar 65	g Phe Thr	Ile Ser 70	Arg Asp Asr	Ser Lys As 75	n Thr Leu Tyr 80
	Leu Gln Me	t Asn Ser 85	_	Ala Glu Asp 90		l Tyr Tyr Cys 95
35	Ala Lys As	p Arg Leu 100	Phe Met	Ser Asp Ser 105	Thr Phe As	p Tyr Trp Gly 110
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55	Ser Leu Ar	g Leu Ser 20	Cys Ala	Ala Ser Gly 25	Phe Thr Ph	e Ser Asp Tyr 30
	Asp Met Se	r Trp Val	Arg Gln	Ala Pro Gly	Lys Gly Le	u Glu Trp Val

		35		40		•	15
	Ser Ala 50	Ile Tyr	Tyr Asp	Ser Gly 55	Ser Ile	Tyr Tyr A	la Asp Ser Ala
5	Lys Gly 65	Arg Phe	Thr Ile	_	Asp Asn	Ser Lys A:	on Thr Leu Tyr 80
10	Leu Gln	Met Asn	Ser Leu 85	Arg Ala	Glu Asp 90	Thr Ala Va	al Tyr Tyr Cys 95
	Ala Lys	Asp Arg 100	Leu Phe	Ala Ser	Asp Ser 105	Thr Phe A	p Tyr Trp Gly 110
15	Gln Gly	Thr Leu 115	Val Thr	Val Ser 120	Ser		
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30	Ser Leu	Arg Leu 20	Ser Cys	Ala Ala	Ser Gly 25	Phe Thr Pl	ne Ser His Tyr 30
	Asp Met	Ser Trp 35	Val Arg	Gln Ala 40	Pro Gly		eu Glu Trp Val 15
35	Ser Ala 50		Tyr Asp	Ser Gly 55	Ser Ile	Tyr Tyr A	la Asp Ser Ala
	Lys Gly 65	Arg Phe	Thr Ile 70	_	Asp Asn	Ser Lys A: 75	sn Thr Leu Tyr 80
40	Leu Gln	Met Asn	Ser Leu 85	Arg Ala	Glu Asp 90	Thr Ala Va	al Tyr Tyr Cys 95
	Ala Lys	Asp Arg 100	Leu Phe	Ala Ser	Asp Ser 105	Thr Phe A	sp Tyr Trp Gly 110
45	Gln Gly	Thr Leu 115	Val Thr	Val Ser 120	Ser		
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5	Ser Leu	Arg Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30	Tyr	Tyr
	Asp Met	Ser Trp 35	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 4 5	Glu	Trp	Val
10	Ser Ala 50	Ile Tyr	Tyr	Asp	Ser 55	Gly	Ser	Ile	Tyr	Tyr 60	Ala	Asp	Ser	Ala
	Lys Gly 65	Arg Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
15	Leu Gln	Met Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
	Ala Lys	Asp Arg 100	Leu	Phe	Ala	Ser	Asp 105	Ser	Thr	Phe	Asp	Tyr 110	Trp	Gly
20	Gln Gly	Thr Leu 115	Val	Thr	Val	Ser 120	Ser							
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30	<223>	Heavy	chali	n var	labl	le re	egior	ı of	anti	rpodi	7 45.	LM5		
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35	Glu Val 1		5					10					15	_
	Glu Val 1 Ser Leu	Gln Leu	5 Ser	Cys	Ala	Ala	Ser 25	10	Phe	Thr	Phe	Ser 30	15 Asp	Tyr
35	Glu Val 1 Ser Leu Asp Met	Arg Leu 20 Ser Trp	5 Ser Val	Cys Ar g	Ala Gln	Ala Ala 40	Ser 25 Pro	Gly	Phe Lys	Thr Gly	Phe Leu 45	Ser 30 Glu	15 Asp Trp	Tyr Val
40	Glu Val 1 Ser Leu Asp Met Ser Ala 50	Arg Leu 20 Ser Trp 35	5 Ser Val Tyr	Cys Arg Asp	Ala Gln Ser 55	Ala Ala 40 Gly	Ser 25 Pro	10 Gly Gly Ile	Phe Lys Tyr	Thr Gly Tyr 60	Phe Leu 45 Ala	Ser 30 Glu Asp	15 Asp Trp Ser	Tyr Val Ala
	Glu Val 1 Ser Leu Asp Met Ser Ala 50 Lys Gly 65	Arg Leu 20 Ser Trp 35	5 Ser Val Tyr	Cys Arg Asp Ile 70	Ala Gln Ser 55	Ala 40 Gly Arg	Ser 25 Pro Ser	10 Gly Gly Ile	Phe Lys Tyr Ser	Thr Gly Tyr 60	Phe Leu 45 Ala Asn	Ser 30 Glu Asp	15 Asp Trp Ser	Tyr Val Ala Tyr 80
40	Glu Val 1 Ser Leu Asp Met Ser Ala 50 Lys Gly 65 Leu Gln	Arg Leu 20 Ser Trp 35 Ile Tyr Arg Phe	5 Ser Val Tyr Thr	Cys Arg Asp Ile 70 Leu	Ala Gln Ser 55 Ser	Ala 40 Gly Arg	Ser 25 Pro Ser Asp	Gly Gly Ile Asn Asp	Phe Lys Tyr Ser 75	Thr Gly Tyr 60 Lys	Phe Leu 45 Ala Asn	Ser 30 Glu Asp Thr	15 Asp Trp Ser Leu Tyr 95	Tyr Val Ala Tyr 80 Cys
40 45	Glu Val 1 Ser Leu Asp Met Ser Ala 50 Lys Gly 65 Leu Gln Ala Lys	Arg Leu 20 Ser Trp 35 Ile Tyr Arg Phe Met Asn Asp Arg	5 Ser Val Tyr Thr Ser 85 Leu	Cys Arg Asp Ile 70 Leu Phe	Ala Gln Ser 55 Ser Arg	Ala 40 Gly Arg Ala	Ser 25 Pro Ser Asp Glu Asp 105	Gly Gly Ile Asn Asp	Phe Lys Tyr Ser 75	Thr Gly Tyr 60 Lys	Phe Leu 45 Ala Asn	Ser 30 Glu Asp Thr	15 Asp Trp Ser Leu Tyr 95	Tyr Val Ala Tyr 80 Cys

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45	Asp Met	Ser Trp Val 35	Arg Gln Ala Pro G 40	ly Lys Gly Leu Glu Trp Val 45			
15	Ser Ala 50	Ile Tyr Tyr	Asp Ser Gly Ser I 55	le Tyr Tyr Ala Asp Ser Ala 60			
20	Lys Gly 65	Arg Phe Thr	Ile Ser Arg Asp A	sn Ser Lys Asn Thr Leu Tyr 75 80			
	Leu Gln	Met Asn Ser 85	_	sp Thr Ala Val Tyr Tyr Cys 90 95			
25	Ala Lys	Asp Arg Leu 100	Phe Glu Ser Asp S 105	er Thr Phe Asp Tyr Trp Gly 110			
	Gln Gly	Thr Leu Val 115	Thr Val Ser Ser 120				
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	Ser Ala 50	Ile Tyr Tyr	Asp Ser Gly Ser I 55	le Tyr Tyr Ala Asp Ser Ala 60			
50	Lys Gly 65	Arg Phe Thr	Ile Ser Arg Asp A	sn Ser Lys Asn Thr Leu Tyr 75 80			
	Leu Gln	Met Asn Ser 85	=	sp Thr Ala Val Tyr Tyr Cys 90 95			
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120

Gln Gly Thr Leu Val Thr Val Ser Ser

115

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20	Ser Val	Ser Trp Tyr 35	Gln Gln	Leu Pro Gly 40	Thr Ala Pro Lys 45	Leu Leu
	Ile Tyr 50	Ser Asp Asn	His Arg 55	Pro Ser Gly	Val Pro Asp Arg 60	Phe Ser
25	Gly Ser 65	Lys Ser Gly	Thr Ser 70	Ala Ser Leu	Ala Ile Ser Gly 75	Leu Arg 80
	Ser Glu	Asp Glu Ala 85	Asp Tyr	Tyr Cys Ala 90	Ala Trp Asp Ser	Ser Leu 95
30	Ser Gly	Tyr Val Phe 100	Gly Gly	Gly Thr Lys 105	Leu Thr Val Leu 110	Gly
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	Ser Val	Ser Trp Tyr 35	Gln Gln	Leu Pro Gly 40	Thr Ala Pro Lys 45	Leu Leu
50	Ile Tyr 50	Ser Asp Asn	His Arg 55	Pro Ser Gly	Val Pro Asp Arg 60	Phe Ser
	Gly Ser 65	Lys Ser Gly	Thr Ser 70	Ala Ser Leu	Ala Ile Ser Gly 75	Leu Arg 80
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Ser Gly His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly 100 105 110

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20	Ser Val	Ser Trp Tyr 35	Gln Gln Leu P: 40	ro Gly Thr Ala	Pro Lys Leu Leu 45
	Ile Tyr 50	Ser Asp Asn	His Arg Pro Se	er Gly Val Pro 60	Asp Arg Phe Ser
25	Gly Ser 65	Lys Ser Gly	Thr Ser Ala Se	er Leu Ala Ile 75	Ser Gly Leu Arg 80
	Ser Glu	Asp Glu Ala 85	Asp Tyr Tyr C	ys Ala Ala Trp 90	Asp Ser Ser Leu 95
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50	Ser Val	Ser Trp Tyr 35	Gln Gln Leu P: 40	ro Gly Thr Ala	Pro Lys Leu Leu 45
	Ile Tyr 50	Ser Asp Asn	His Arg Pro Se 55	er Gly Val Pro 60	Asp Arg Phe Ser
55	Gly Ser 65	Lys Ser Gly	Thr Ser Ala So	er Leu Ala Ile 75	Ser Gly Leu Arg 80
	Ser Glu	Asp Glu Ala	Asp Tyr Tyr C	ys Ala Ala Trp	Asp Ser Ser Leu

					85					90					95	
	Ser	Gly	Tyr	Val	Phe	Gly	Gly	Gly	Thr 105	Lys	Leu	Thr	Val	Leu 110	Gly	
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Claims

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- 1. A pharmaceutical composition for use in the prevention or treatment of a cancer or anti-cancer drug resistance, the pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof that specifically binds to ErbB3, comprising heavy chain complementarity determining regions (CDR-Hs) and light chain complementarity determining regions (CDR-Ls), wherein the antibody is selected from the group consisting of:
 - (1) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 70, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 95.
 - (2) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 73, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 94;
 - (3) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 74, a CDR-H3 having the sequence of SEQ ID NO: 79, a CDR-L1 having the sequence of SEQ ID NO: 87, a CDR-L2 having the sequence of SEQ ID NO: 89, and a CDR-L3 having the sequence of SEQ ID NO: 94;
 - (4) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 63, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100;
 - (5) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 66, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100.
- 2. The pharmaceutical composition of claim 1, wherein the cancer is selected from the group consisting of breast cancer, skin cancer, head and neck cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, gastric cancer, ovarian cancer, prostate cancer, bladder cancer, uterine cancer, liver cancer, kidney cancer, clear cell sarcoma, melanoma, cerebrospinal tumors, brain cancer, thymoma, mesothelioma, esophageal cancer, biliary tract cancer, testicular cancer, germinal cancer, thyroid cancer, parathyroid cancer, cervical cancer, endometrial cancer, lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, acute leukemia, chronic leukemia, multiple myeloma, Hodgkin's disease, endocrine cancer, and sarcoma.
 - 3. The pharmaceutical composition of any one of claims 1 to 2, further comprising an anti-cancer drug.

- **4.** The pharmaceutical composition of claim 3, wherein the anti-cancer drug is Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab, T-DM1, Pertuzumab, Lapatinib, Paclitaxel, Tamoxifen, Cisplatin, anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-LI antibody, 5-fluorouracil (5FU), Gemcitabine, or a combination thereof.
- 5 The pharmaceutical composition of claim 4, wherein the pharmaceutical composition further comprises a single composition or separate compositions.

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- **6.** An antibody or antigen-binding fragment thereof for use in the prevention or treatment of a cancer or anti-cancer drug resistance in an individual, the antibody or the antigen-binding fragment thereof that specifically binds to ErbB3, comprising heavy chain complementarity determining regions (CDR-Hs) and light chain complementarity determining regions (CDR-Ls), wherein the antibody is selected from the group consisting of:
 - (1) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 70, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 95:
 - (2) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 73, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 94:
 - (3) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 74, a CDR-H3 having the sequence of SEQ ID NO: 79, a CDR-L1 having the sequence of SEQ ID NO: 87, a CDR-L2 having the sequence of SEQ ID NO: 89, and a CDR-L3 having the sequence of SEQ ID NO: 94;
- (4) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 63, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100;
 - (5) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 66, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100.
- 7. The antibody or antigen-binding fragment thereof for use according to claim 6, further comprising administering an anti-cancer drug to the individual.

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FIG. 1A CDR1 CDR2 CDR3 Antibody $evollesggglvqpggslrlscaasgftfs \underline{\hspace{-0.05cm}}\underline{\hspace{-0.05cm$ -GPFDYWGQGTLVTVSS 442P evollesggglvopggsirlscaasgfffs<mark>dydms</mark>wrqapgkglewy<u>stidldsgstyyadsvog</u>rftisrdnskntlylomnslraedtavyycak<mark>dl+mgpe</mark> evollesggglvopggsirlscaasgfffs<u>dydms</u>wrqapgkglewy<u>stypdsgstdyadsvog</u>rftisrdnskntlylomnslraedtavyycak<u>Dl+mgp</u>i -GPFDYWGQGTLVTVSS 442S1 -GPFDYWGQGTLVTVSS 44252 EVOLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSSIEPDFGSSYYADSVRGPFTISRDNSKNTLYLQMNSLRAEDTAVYYCAMDLHMGPE -GPFDYWGQGTLVTVSS 442S4 EVOLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWYRQAPGKGLEWYSLEPDSGSIYYADSVQGRFTISRDNSKYTLYLQMNSLRAEDTAVYYCAKDLHMGPE— EVOLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWYRQAPGKGLEWYSIYPDSGSTDYADSVQGRFTISRDNSKYTLYLQMNSLRAEDTAVYYCAKDRHMWPE EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWYRQAPGKGLEWYSIYPDSGSTYYADSVQGPFTISRDNSKYTLYLQMNSLRAEDTAVYYCAKDRHMWPE 442S5 <u>GPFDY</u>WGQGTLVTVSS -GPFDYWGQGTLVTVSS 44286 GPFDYWGQGTLVTVSS 44289 EVOLLESGGGLVOPGGSLRLSCAASGFTFSDYDMSWYROAPGKGLEWYSSIYPDSGSTYYADSVQGPFTISRDNSKNTLYLOMNSLRAEDTAVYYCAKDRHMWPE EVOLLESGGGLVOPGGSLRLSCAASGFTFSDYDMSWYROAPGKGLEWYSSIYPDSGSTYYADSVQGPFTISRDNSKNTLYLOMNSLRAEDTAVYYCAKDRHMWPE EVOLLESGGGLVOPGGSLRLSCAASGFTFSDYDMSWYROAPGKGLEWYSTIDLDSGSIYYADSVQGPFTISRDNSKNTLYLOMNSLRAEDTAVYYCAKDLHMGPE--GPFDYWGQGTLVTVSS 442510 -GPFD\WGQGTLVTVSS 442M3 -GPFDYWGQGTLVTVSS 442M4 EVOLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWYRQAPGKGLEVW9TIDLDSGSIYYADSVQQRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLHMGPE -GPFDYWGQGTLVTVSS 442M5 442M6 -GPFDYWGQGTLVTVSS 442M7 EVOLLESGGGLVQPGGSLRLSCAASGFTFS<mark>DYDMS</mark>WVRQAPGKGLEVVYS<mark>TIEPDSGSTYYADSVQS</mark>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLHMGPE **GPFDYWGQGTLVTVSS** EVQLLESGGGLVQPGGSLRLSCAASGFTFS<mark>DYDMS</mark>WYRCAPGKGLEWYS<mark>SYYDSGSTYYADSVQQ</mark>RFTISRDNSKNTLYLQMNSLRAEDTAWYCAY<mark>DLHMGP</mark>F -GPFDYWGQGTLVTVSS 442M8 442M10 -GPFDYMGQGTLVTVSS GPFDYWGQGTLVTVSS EVOLLESGGGLVQPGGSLRLSCAASGFTFS<mark>DYDMS</mark>MVRQAPGKGLEWVS<u>TIEPDYGSTLYADSVQG</u>RFTISRDNSKNTLYLQMINSLRAEDTAVYYCAK<mark>DLHMGPE</mark> 442M11 EVQLLESGGGLVQPGGSLRLSCAASGFTF\$DYDM\$WYRQAPGKGLEWV\$GISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAFDP\$WCLQDLCYYADGMDYWGQGTLVTVSS 472P EVOLLESGGGLVQPGGSLRLSCAASGFTF\$WYDMTWVRQAPGKGLEWV\$GISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAFDPSWCLQDLCYYADGMDYWGQGTLVTVSS 472S1 EVQLLESGGGLVQPGGSLRLSCAASGFTF\$WYDLAWVRQAPGKGLEWV\$GISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAPDPSWCLQDLCYYADGMDYNGQGTLYTV\$\$ 47282 EVOLLESGGGLVQPGGSLRLSCAASGFTFS<u>WYDMS</u>WVRQAPGKGLEWVS<u>GISYDGGNTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<mark>DPSWCLQDLCYYADGMDW</mark>WGQGTLVTVSS EVOLLESGGGLVQPGGSLRLSCAASGFTFS<u>WYDM</u>WVRQAPGKGLEWVS<u>GISYDGGNTYYADSVKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR<u>DPSWCLQDLCYYADGMDW</u>WGQGTLVTVSS 472S3 47284 472M1 evgllesggglvqpggslrlscaasgftfs<u>wydls</u>wrqapgkglews<u>gisydggntyyadsvkg</u>rftisrdnskntlylqmnslaedtavyycaf<u>dpswclqdlcyyadgmd</u>wgggtlvtvss EVOLLESGGGLVQPGGSLRLSCAASGFTF5DYDMSWVRQAPGKGLEWWSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAMDRLFVSD-451P -STFDYWGOGTLVTVSS EVOLLESGGGLVQPGGSLRLSCAASGFTF5DYDMSWVRQAPGKGLEWV9AIYYDSGSYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFMSD--STFDYWGQGTLVTVSS 451M1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSQVDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFASD -STFDYWGQGTLVTVSS 451M2 ${\tt evollesggglvqpggslrlscaasgfff} \underline{{\tt hydm}} \underline{{\tt hydmp}} \underline{{\tt hydmp}} \underline{{\tt hydmp}} \underline{{\tt hydgs}} \underline{{\tt hydg$ STFDYWGQGTLVTVSS 451M3 451M4 <u>STFDY</u>WGQGTLVTVSS EVQLLESGGGLVQPGGSLRLSCAASGFTF<u>\$DYDM\$</u>WVRQAPGKGLEWV<u>\$AYYDSGSIYYADSAKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK<u>DRLFESD</u> EVQLLESGGGLVQPGGSLRLSCAASGFTF<u>\$HYDM\$</u>WVRQAPGKGLEWV<u>\$AYYDSGSIYYADSAKG</u>RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK<u>DRLFESD</u> 451M6 STFDYWGQGTLVTVSS STFDYWGQGTLVTVSS 451M6 EVOLLESGGGLVQPGGSLRLSCAASGFTFSYYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFESD--STFDYWGQGTLVTVSS 451M7

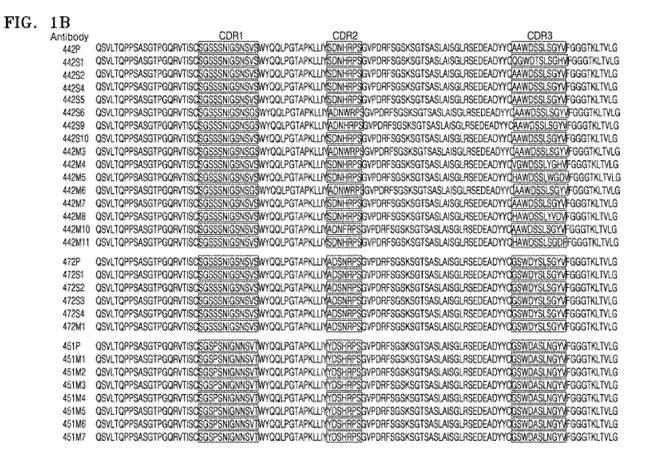
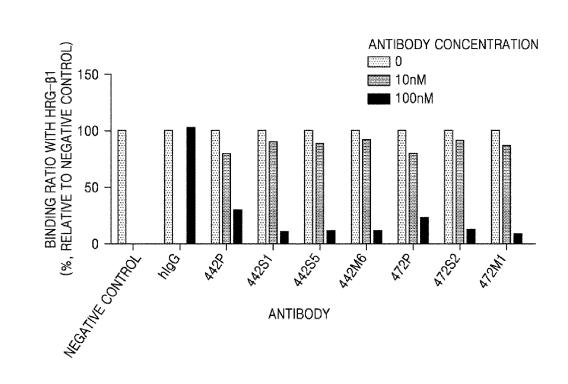


Figure 2



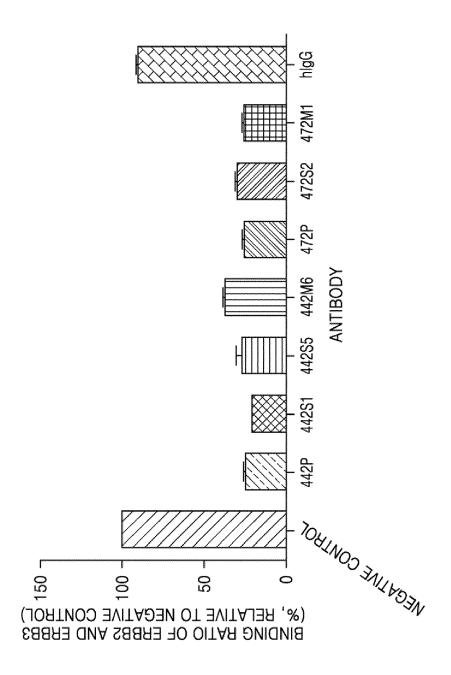
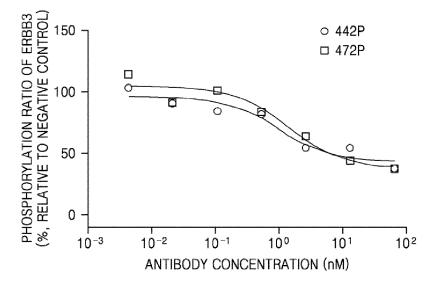


Figure 4A



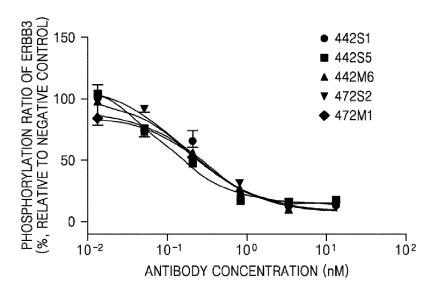


Figure 4B

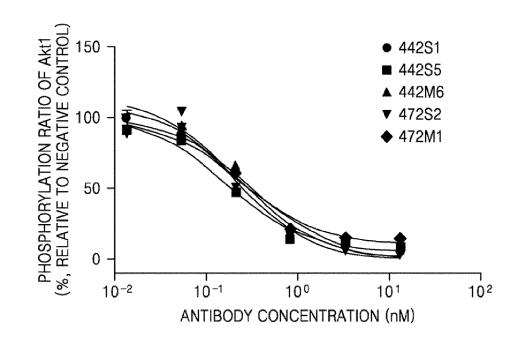


Figure 5

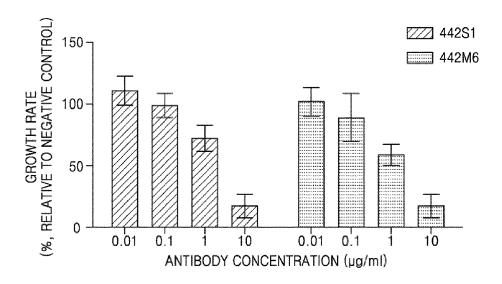


Figure 6

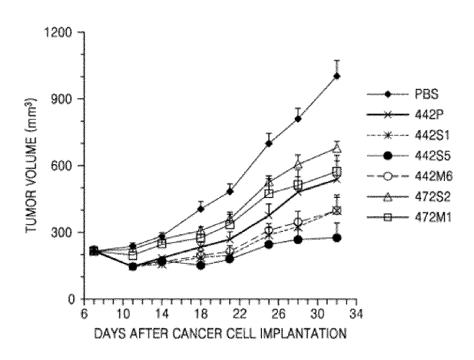


Figure 7

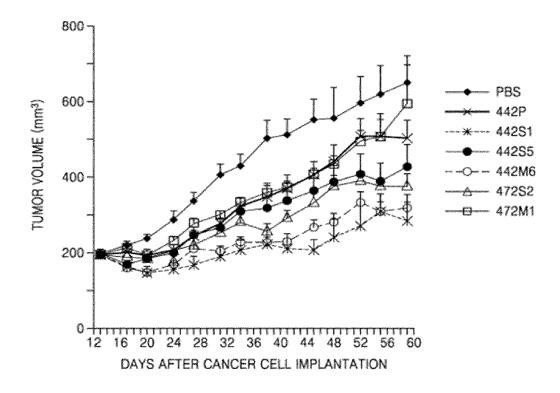


Figure 8

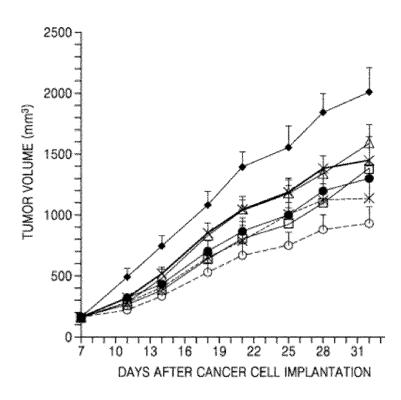


Figure 9

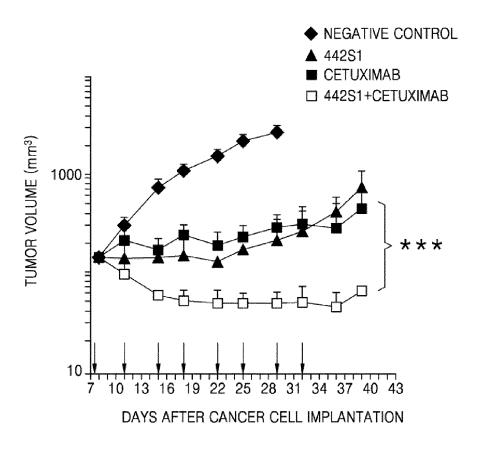


Figure 10

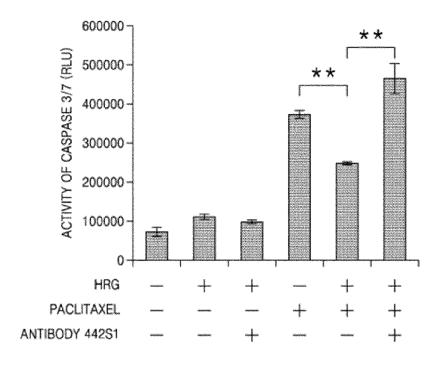


Figure 11

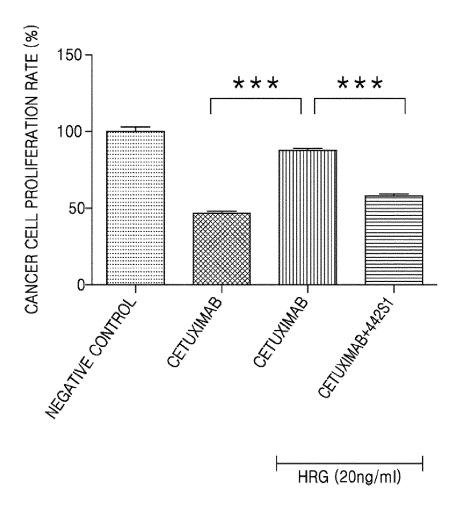
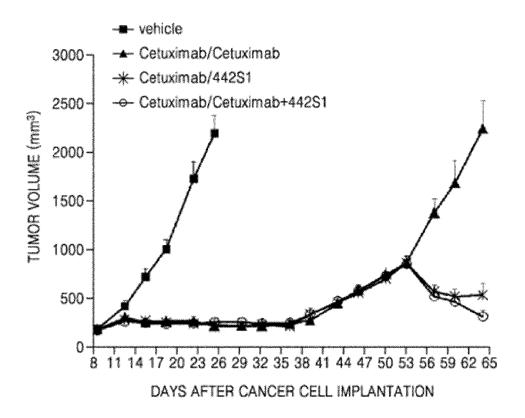


Figure 12





Category

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C07K16/32

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A61K31/00 A61P35/00

A61K39/395

TECHNICAL FIELDS SEARCHED (IPC)

C07K

A61K

A61P

Relevant

to claim

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The present search report has	been drawn up for all claims	
Place of search	Date of completion of the search	Examiner
The Hague	18 December 2020	Luyten, Kattie
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